Assessing the effects of crew exposure to cabin altitudes of 8,000 ft to 10,000 ft

A literature review and recommendations

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Abstract

Introduction. In an effort to prolong airframe life of E model CC130 aircraft, cabin pressure has been degraded to 10 PSI from the normal 15.3 PSI. This has resulted in higher cabin altitudes at operational altitudes. Whereas at normal operational altitudes, cabin altitudes used to be in the 1,500 ft range, they are now between 8,000 ft and 10,000 ft. Such cabin altitudes have recently provoked 2 physiologic incidents. Acute Mountains Sickness (AMS) has been reported at altitudes as low as 6,500 ft. This report will review the literature on AMS and will address the issue of risk management for aircrews flying at cabin altitudes between 8,000 ft and 10,000 ft.

Review of AMS. Essentially, travelling too quickly to altitudes over 8,000 ft often results in symptoms of AMS with nearly 25% of persons affected at 6,500 ft. Incidence and severity of AMS vary with rate of ascent, altitude attained, time at altitude and original altitude. AMS symptoms can start to appear within 5 to 6 hours of exposure to altitude. If ascent is halted, AMS usually resolves within 1-2 days, but substantial discomfort and inconvenience are commonly encountered. Above 13,000 ft, the life threatening high altitude pulmonary (HAPE) and/or cerebral (HACE) edema occurs in about 5% of those afflicted with AMS. While there are several different theories as to the mechanism on onset of AMS, the exact cause remains unclear. Certainly, the hypoxia and hypercapnia that are brought on by unprotected exposure to altitude result in vasodilatation that in turn increases cerebral blood flow. The blood-brain barrier (BBB) may be altered in hypoxia and may facilitate increase cerebral blood volume as well as intracranial pressure and may explain swollen and edematous brains on autopsy. Craniospinal capacitance (the ability to shunt cerebrospinal fluid from the brain to the spinal canal in response to raised intracranial pressure) may prevent or attenuate AMS sysmptoms. Individual differences in susceptibility to AMS may be due to random anatomical differences between people such that people with a smaller intracranial and intraspinal CSF (cerebrospinal fluid) capacity could be at higher risk to develop AMS given that they would not be able to tolerate brain selling as well as people with more 'room' in the craniospinal axis. Recently treatments for AMS involve reduction of sympathetic activity by treatment with clonidine or propranolol (2 medications used to reduce blood pressure) or by use of Gingko Biloba that is thought to reduce BBB opening in AMS. The risk of developing AMS is difficult to predict because of large inter-individual differences in susceptibility to AMS. However the various studies have demonstrated AMS in significant proportion of individuals in the 8,000 ft to 10,000 ft range.

Review of impact of hypoxia on performance. During the 1960s and 1970s a debate as to whether or not performance is compromised at 8,000 ft appeared in the literature. Most of this work suggesting that performance is compromised at 8,000 ft and that performance of complex unlearned tasks can be impaired as low as 5,000 ft came from the R.A.F. Institute of Aviation Medicine in Farnborough. Work done in the 1990s at DRDC Toronto has refuted those findings. The minimum altitude at which hypoxia-induced decrements in performance can be detected has been a controversial issue. However, the most recent evidence suggests that between 8,000 and 10,000 ft, the risk while real, is relatively low.

Recommendations to mitigate risk of AMS between 8,000 and 10,000 ft. Exposure time to these cabin altitudes should be limited to 4 hours. If operational requirements dictate longer exposure, supplementary oxygen should be provided. in this case, a low-flow pulse-dose oxygen sparing system delivered via oro-nasal cannula is recommended.

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Résumé

Introduction. Dans un effort visant à prolonger la durée de vie de la cellule du modèle E de l'avion CC130, on a diminué la pressurisation de la cabine pour la faire passer de 15,3 lb/po^2 à 10 lb/po^2. Il s'en est suivi des altitudes cabine plus élevées aux altitudes opérationnelles. Alors qu'aux altitudes opérationnelles normales, les altitudes cabine se tenaient autour de 1 500 pi, elles se situent maintenant entre 8 000 et 10 000 pi. De telles altitudes cabine ont provoqué récemment deux incidents physiologiques. Le mal d'altitude a été signalé à des altitudes d'à peine 6 500 pi. Le présent rapport passe en revue la documentation sur le mal d'altitude et traite de la question de la gestion des risques pour le personnel navigant volant à des altitudes cabine comprises entre 8 000 et 10 000 pi.

Revue du mal d'altitude. Essentiellement, le fait d'accéder trop rapidement à des altitudes supérieures à 8 000 pi se traduit souvent par l'apparition des symptômes du mal d'altitude, près de 25 % des sujets étant touchés à 6 500 pi. L'incidence et la gravité du mal d'altitude varient selon le taux de montée, l'altitude atteinte, la durée en altitude et l'altitude de départ. Les symptômes du mal d'altitude peuvent commencer à apparaître dans les 5 ou 6 heures suivant l'exposition à l'altitude. Si la montée s'arrête, les symptômes disparaissent au bout de 1 ou de 2 jours, mais un inconfort et des malaises importants surviennent fréquemment. Au-dessus de 13 000 pi, un œdème pulmonaire à haute altitude ou un œdème cérébral à haute altitude, ou les deux, se produisent chez environ 5 % des sujets victimes du mal d'altitude et risquent de mettre leur vie en danger. Il existe plusieurs théories sur le mécanisme qui intervient lors de l'apparition du mal d'altitude, mais la cause exacte n'est toujours pas connue. Chose certaine, l'hypoxie et l'hypercapnie causées par une exposition sans protection à l'altitude se traduisent par une vasodilatation qui, à son tour, augmente le flux sanguin cérébral. La perméabilité de la barrière hémato-encéphalique peut être altérée sous l'effet de l'hypoxie, ce qui risque d'entraîner une augmentation du volume sanguin cérébral et de la pression intracrânienne, et peut expliquer la présence d'une enflure ou d'un œdème cérébral à l'autopsie. La capacité de faire dévier le liquide céphalorachidien du cerveau dans le canal rachidien en réaction à une augmentation de la pression intracrânienne peut prévenir l'apparition des symptômes du mal d'altitude ou atténuer ces derniers. Les différences individuelles dans la susceptibilité au mal d'altitude peuvent être dues à des différences anatomiques fortuites; ainsi, des sujets chez qui circule moins de liquide céphalorachidien dans le crâne et la moelle épinière pourraient être plus susceptibles de souffrir du mal d'altitude, compte tenu du fait qu'ils ne pourraient tolérer un œdème cérébral aussi bien que ceux dont l'axe céphalorachidien présente « plus d'espace ». De récents traitements pour le mal d'altitude reposent sur une réduction de l'activité du système sympathique au moyen d'un traitement à la clonidine ou au propranolol (deux médicaments utilisés pour réduire la tension artérielle), ou au moyen de gingko biloba, qui est réputé réduire la perméabilité de la barrière hémato-encéphalique lors du mal d'altitude. Le risque de souffrir du mal d'altitude est difficile à prédire en raison des grandes différences de susceptibilité entre les individus. Toutefois, diverses études ont montré que le mal d'altitude survient chez une proportion importante d'individus exposés à des altitudes comprises entre 8 000 et 10 000 pi.

Revue de l'incidence de l'hypoxie sur la performance. Au cours des années 1960 et 1970, on a commencé à s'interroger dans la documentation scientifique sur la possibilité que la performance soit perturbée à une altitude de 8 000 pieds. La plupart des travaux soutenant que la performance était altérée à 8 000 pieds et que l'exécution de tâches complexes non apprises pouvait être perturbée à une altitude d'à peine 5 000 pieds provenaient de l'institut de

médecine aéronautique de la RAF, à Farnborough. Des travaux effectués à la RDDC Toronto dans les années 1990 ont réfuté ces conclusions. L'altitude minimale à laquelle une dégradation de la performance induite par l'hypoxie peut être détectée est une question qui a fait l'objet de controverses. Cependant, des travaux plus récents laissent entendre qu'entre 8 000 et 10 000 pi le risque est réel, mais relativement faible.

Recommandations visant à réduire le risque de mal d'altitude à une altitude de 8 000 à 10 000 pi. La durée d'exposition à ces altitudes cabine devrait être limitée à quatre heures. Si les exigences opérationnelles imposent une plus longue exposition, de l'oxygène supplémentaire devrait être fourni. Dans ce cas, il est recommandé que de l'oxygène à faible débit et à dose pulsée soit administré au moyen d'une canule oro-nasale.

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Executive summary

In an effort to prolong airframe life of E model CC130 aircraft, cabin pressure has been degraded to 10 PSI from the normal 15.3 PSI. This has resulted in higher cabin altitudes at operational altitudes. Whereas at normal operational altitudes, cabin altitudes used to be in the 1,500 ft range, they are now between 8,000 ft and 10,000 ft. Such cabin altitudes have recently provoked 2 physiologic incidents. Acute Mountains Sickness (AMS) has been reported at altitudes as low as 6,500 ft. This report will review the literature on AMS and will address the issue of risk management for aircrews flying at cabin altitudes between 8,000 ft and 10,000 ft.

Essentially, travelling too quickly to altitudes over 8,000 ft often results in symptoms of AMS with nearly 25% of persons affected at 6,500 ft. Incidence and severity of AMS vary with rate of ascent, altitude attained, time at altitude and original altitude. AMS symptoms can start to appear within 5 to 6 hours of exposure to altitude. If ascent is halted, AMS usually resolves within 1-2 days, but substantial discomfort and inconvenience are commonly encountered. Above 13,000 ft, the life threatening high altitude pulmonary (HAPE) and/or cerebral (HACE) edema occurs in about 5% of those afflicted with AMS. While there are several different theories as to the mechanism on onset of AMS, the exact cause remains unclear. Some possible theories on the causes of AMS are reviewed. The risk of developing AMS is difficult to predict because of large inter-individual differences in susceptibility to AMS. However the various studies have demonstrated AMS in significant proportion of individuals in the 8,000 ft to 10,000 ft range.

During the 1960s and 1970s a debate as to whether or not psychomotor performance is compromised at 8,000 ft appeared in the literature. Most of this work suggesting that performance is compromised at 8,000 ft and that performance of complex unlearned tasks can be impaired as low as 5,000 ft came from the R.A.F. Institute of Aviation Medicine in Farnborough. Work done in the 1990s at DRDC Toronto has refuted those findings. The minimum altitude at which hypoxia-induced decrements in performance can be detected has been a controversial issue. However, the most recent evidence suggests that between 8,000 and 10,000 ft, the risk while real, is relatively low.

Exposure time to these cabin altitudes should be limited to 4 hours. If operational requirements dictate longer exposure, supplementary oxygen should be provided. In this case, a low-flow pulse-dose oxygen sparing system delivered via oro-nasal cannula is recommended. Such a system is can provide oxygen for 43 hours at normal cockpit workload. Given that the average flying time for a re-supply mission from Trenton to Bosnia is about 30 to 33 hours, this system could easily provide continuous oxygen for the full duration of such a mission.

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Sommaire

Dans un effort visant à prolonger la durée de vie de la cellule du modèle E de l'avion CC130, on a diminué la pressurisation de la cabine pour la faire passer de 15,3 lb/po^2 à 10 lb/po^2. Il s'en est suivi des altitudes cabine plus élevées aux altitudes opérationnelles. Alors qu'aux altitudes opérationnelles normales, les altitudes cabine se tenaient autour de 1 500 pi, elles se situent maintenant entre 8 000 et 10 000 pi. De telles altitudes cabine ont provoqué récemment deux incidents physiologiques. Le mal d'altitude a été signalé à des altitudes d'à peine 6 500 pi. Le présent rapport passe en revue la documentation sur le mal d'altitude et traite de la question de la gestion des risques pour le personnel navigant volant à des altitudes cabine comprises entre 8 000 et 10 000 pi.

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La durée d'exposition à ces altitudes cabine devrait être limitée à quatre heures. Si les exigences opérationnelles imposent une plus longue exposition, de l'oxygène supplémentaire devrait être fourni. Dans ce cas, il est recommandé que de l'oxygène à faible débit et à dose pulsée soit administré au moyen d'une canule oro-nasale. Un tel dispositif peut fournir de l'oxygène pendant 43 heures pour une charge de travail normale en poste de pilotage. Compte tenu du fait que le temps de vol moyen pour une mission de réapprovisionnement entre Trenton et la Bosnie est d'environ 30 à 33 heures, ce dispositif pourrait facilement fournir de l'oxygène en continu pour toute la durée d'une telle mission.

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1. Introduction

Subsequent to an 8 AMS (Air Maintenance Squadron) engineering order (1) calling for the reduction of cabin pressure to 10 PSI from the normal 15.3 PSI capability of E model CC130 aircraft, at normal service altitudes, cabin altitudes increased to between 8,000 ft to 10,000 ft. Prior to the engineering order, at operational altitudes, cabin altitudes were in the 1,500 ft range. Such higher cabin altitudes resulted in 2 physiologic incidents on board these older model CC130 aircraft (2, 3). DCIEM (now DRDC Toronto) was tasked to monitor blood oxygen levels on such an aircraft during a routine air transport mission to Bosnia in March 2001. The resulting report (66) confirmed that the crews were being exposed to altitudes resulting in mild hypoxia.

In response to the report (66) 1 CAD requested DRDC Toronto to conduct a literature review on the effects of mild hypoxia including Acute Mountain Sickness (AMS) and to provide recommendations for changes to Routine Flying Orders to mitigate such risks in CC130 aircrew.

Approximately 30 million people are at risk for altitude-related illnesses in the western United States each year (5). Many cases are unrecognized by the visitors or by their physicians who often confound symptoms of altitude illnesses with viral illness, hangover, or fatigue (49). The rate of altitude-related illness increases proportionally with the exposure altitude. Approximately 20% of tourists to Colorado ski resorts (elevation about 3,000 m. or 10,000 ft.) experience acute mountain sickness (40) compared to 67% of the climbers on Mount Rainier (elevation 4,500 m. or 14,800 ft) (84). Approximately 0.01% of tourists to Colorado ski resorts will experience pulmonary edema (HAPE) or high-altitude cerebral edema (HACE) (43).

This report will briefly review the literature on mountain sickness and address the issue of risk management in the context of aircrews flying at cabin altitudes between 8,000 ft and 10,000 ft. Also, this report will offer some recommendations with respect to modification of CF Routine Flying Orders with respect to maximum exposure times to cabin altitudes in this range, and will suggest evaluation of a new type of oxygen delivery system to cover the possibility that the aircrews will have to endure elevated cabin altitudes for longer than the recommended times.

2. A history of mountain sickness

The earliest description of AMS (Acute Mountain Sickness) was recorded by Chinese travelers in approximately 30 B.C. when they made reference to the "Great Headache Mountain and the Little Headache Mountain" (91). The Inca civilization that flourished on the Andean Altiplano between A.D. 1100 and 1532 knew AMS as soroche, and their Amaryan neighbours living around Lake Titicaca, called it puna. Both these Indian cultures knew the cure for AMS was coca leaves. The Incas had no written language, and it was not until the Spaniards had conquered the Inca Empire that the use of coca was first detailed. In 1555, a Spanish Physician, Dr de Zarate, wrote home saying:

.....in certain mountain valleys there grows a plant called coca, which the Indians prize higher than gold or silver. The unique property of this plant, as experience shows, is that whoever chews its leaves feels neither cold, nor hunger, nor thirst.

In 1569, Jose de Acosta, a Jesuit working in Peru noticed severe nausea while riding a donkey at 17,500 ft. He described the first case of soroche as it affected a European and attributed its cause to the rarefied mountain air. Man has subjected himself to hypoxia conditions, not only by climbing mountains, but also by rising to great heights in balloons and airplanes. The Mongolgier brothers made the first balloon flights in 1783. In the ensuing years many observations were made but it was not until 1818 that Paul Bert described the specific effect of altitude on barometric pressure, in his book "La Pression Barometrique" (10). Also in 1818, during an ascent of Mont Blanc, Saussere, postulated that mountain sickness was a result of reduced oxygen pressure at altitude. In 1875 three scientists experimenting with hypoxia, (Sivel, Croce-Spinelli, and Tissandier) ascended to 8,595 meteres (28,200 ft) in the balloon 'Zenith' and only Tissandier survived the adventure (10). In 1898 the Italian physiologist Mosso noted that carbon dioxide was also lost at high altitude because of increased ventilation. In his report he described the death of Dr. Jacottet, a physician from Chamonix who died at 14,300 ft after climbing Mont Blanc. His death may well have been AMS progressing to acute High Altitude Pulmonary Edema (HAPE). In 1911 the Yale expedition to Pikes Peak with Henderson, Schneider, Douglas and Haldane added to the carbon dioxide theory. They concluded that the decrease in carbon dioxide exacerbated the hypoxia by diminishing the normal stimulus to breathing. Hence they postulated that "a deficiency of carbon dioxide leads in turn to a deficiency of oxygen" (20) but which has since been ruled out as a viable theory by more recent investigations. The wide use of airplanes in combat in the First World War resulted in a renewed interest in the study of man's ability to function at high altitude. During this period scientists attempted to develop life support equipment to avoid the effects of acute hypoxia such as shortness of breath, palpitation, headache, nausea, light-headedness, vomiting, mental confusion, muscular weakness, incoordination, cynanosis, and emotional lability (89). The introduction of high performance monoplanes in the Second World War resulted in another series of studies of hypoxia because of the higher altitudes and longer endurance flights that could be achieved with these aircraft. In 1919, Haldane suggested a new approach to the treatment of AMS by using ammonium chloride to acidify the blood and counteract the pH change (37). In 1935, Childes et al reported some success in prevention of AMS by breathing carbon dioxide in order to limit respiratory loss of carbon dioxide (17). Other cures including methylene blue and potassium

chloride were tried but did not prove to be successful. Attention reverted to the blood pH in 1966 when Cain and Dunn (15) used acetazolamide to acidify blood by its inhibition of the carbonic anhydrase enzyme system resulting in a promising treatment to prevent AMS. Their initial results were confirmed in 1968 by Forwand et al (23). The next year, Singh et al. demonstrated success in the prevention of AMS by treatment with the diuretic furosemide in a study over 30,000 Indian troops exposed to high altitude. In 1971 Gray et al (27) demonstrated the AMS prophylactic efficacy of manipulation of blood pH with acetazolamide, but found no evidence of any benefit of countering AMS by diuretic treatment with furosemide.

3. Altitude-related illnesses defined

Ravenhill (69) drafted the original classification of altitude illnesses in 1913. He used the Amarya term of "puna" for altitude illness and classified three types: normal puna, for what is now referred to as acute mountain sickness (AMS), nervous puna, for what is now known as High altitude cerebral edema (HACE), and cardiac puna, for what is now known as high altitude pulmonary edema (HAPE).

AMS.

Acute Mountain Sickness is a syndrome defined by a constellation of symptoms in persons exposed to high altitudes. Symptoms include headache, marked lassitude and fatigue, nausea, and sometimes vomiting and sleep disturbances. AMS symptoms may occur in some individuals as low as 6500 ft but the incidence and severity increase with the altitude of exposure.

HACE.

This more severe form of AMS has prominent neurologic features that in addition to the symptoms of AMS may include severe headache, ataxia, irritability, hallucinations, drowsiness, coma and possible incontinence. This form of altitude illness is closely related to AMS and probably represents the most severe form of this illness (49). HACE can occur in 2 to 3% of climbers at altitudes above 5,500 m. (18,000 ft), however symptoms can occur at any altitude higher than 2,500 m. (8,000 ft) but at a reduced frequency of occurrence (49).

HAPE.

This form of mountain sickness has symptomology dominated by breathlessness, tachypnea, cough, and the production of white frothy or sometimes blood-stained sputum, cyanosis, and crepitations (85). HAPEcan occur at any altitude above 2,500 m. (8,000 ft) and is the most frequent cause of death among the altitude illnesses (49). The incidence of HAPE varies from less than 1 in 10,000 skiers on Colorado to 1 in 50 climbers on Mount McKinley (31).

Since this report is to address the issues of altitude-related illness in the context of cabin altitudes in the range of 8,000 ft to 10,000 ft, the balance of this report will only deal with AMS, since it is highly unlikely that HACE and HAPE would ever occur at these lower altitudes.

4. A review of AMS

Essentially, travelling too quickly to altitudes over 2,500 m. (8,000 ft) often results in symptoms of AMS with nearly 25% of persons affected at 2000 m. (6,500 ft) (34, 50, 51, 63, 83). The incidence and severity vary with rate of ascent, altitude attained, and original altitude. If ascent is halted, AMS usually resolves in 1-2 days, but substantial discomfort and inconvenience are commonly encountered (71). The number of symptoms, as well as severity, rapidity of onset, time course and duration vary widely among individuals (74). AMS usually begins to appear after 6 hours at altitude (16, 74, 90). Fitness is neither predictive nor a risk factor for AMS (61). A study investigating susceptibility to AMS in 558 children at 2,835 m. (9,300 ft) found that 28% of the children developed AMS but 21% of the children at sea level developed similar symptoms, suggesting that an appreciable number of the symptoms present were due to factors other than altitude such as travel anxiety, or disruption of daily routine (87). Ninety-seven older persons ranging in age from 59 to 83 years of age were studied in Vail Colorado for 5 days at 2,500 m. (8,200 ft). The incidence of AMS in these subjects was 16% and somewhat lower than the incidence rate for younger people. Of these older subjects, 20% had coronary artery disease, 34% had hypertension, and 9% had lung disease, suggesting that persons with pre-existing, generally asymptomatic, cardiovascular or pulmonary disease can safely visit moderate altitudes (73). A study of women on oral contraceptives exercising at 4688 m (15,000 ft) had a lower AMS incidence rate than that reported for exercising males, suggesting that the oral contraceptives, may cause a compensation for the physiologic response to exercise critical for the development of AMS (79). Further, above 4,000 m. (13,000 ft) the life threatening pulmonary (HAPE) and/or cerebral (HACE) edema occurs in about 5% of those afflicted with AMS (83).

Table 1. Incidence of Acute Mountain Sickness

AUTHOR (DATE)	LOCATION	ALTITUDE (FT)	PERCENT WITH AMS
Montgomery (1989)	Colorado	6,765	20
		6,900	25
		8,900	40
Houston (1985)	Colorado	8,500	12
		9,500	17
Dean (1990)	Colorado	9,800	42
Marganne (1989)	Alps	6,700	9
		10,000	13
		12,000	34
		15,000	54
Hackett (1976)	Nepal	14,000	42
Hangman (1993)	Colorado	6-7,000	18
		7-9,000	22
		>9,000	27

from C. Houston, 1998 (41)

Various factors have been studied in the pathogenesis of mountain sickness but the cause is still not clear. In a normal person, high altitude increases ventilation, hypocapnia, respiratory alkalosis, and compensatory renal excretion of bicarbonate, which results in a further appropriate increase in ventilatory drive (49). However, inappropriate hypoventilation has been associated with an increased risk of AMS (4, 13, 23, 33, 64). Such hypoventilation at altitude should result in a disproportionate decrease in arterial blood oxygen saturation (SaO_2). Roach et al (71) have demonstrated that at 4,200 m (14,000ft) subjects with an SaO_2 above 84% appear to be immune to the development of AMS.

A normal physiologic response of the CNS to hypoxia and hypercapnia is vasodilation, with an attendant increase in cerebral blood flow (CBF). Several studies have reported an increase in CBF at altitude (6, 44, 81, 83). At 4,559 m. (15,000 ft), Baumgartner et al (7) used Trans Cranial Doppler to demonstrate that the increase in CBF for subjects who developed AMS was significantly higher than for subjects without AMS. Later, Baumgartner et al (8) used an altitude chamber at the same altitude to demonstrate that while CBF can be raised at altitude, it is not important to the pathogenesis of AMS. The latter Baumgartner data (8) and data from two other studies (42, 70) indicate that during the first hours at hypobaric hypoxia CBF may decrease, remain unchanged, or increase, independent of the development of AMS.

Hansen and Evans (38) postulated that AMS results from compression of brain cells. They based this opinion on the evidence that exposure to high altitude causes a shift of water into the brain, as well as elevated cerebrospinal fluid pressure, and elevated CBF. Sutton and Lassen (86) supported this view by proposing that high cerebral hydrostatic pressure resulting from hypoxic vasodilation causes increased capillary filtration similar to vascular "autoregulatory breakthrough" that occurs in hypertensive encephalopathy (45). Sutton and Lassen (86) suggested that blood-brain barrier (BBB) permeability is altered and that high cerebral hydrostatic pressure may be further increased by arterial blood pressure increases during exercise or cold.

Through the compensatory mechanisms of increased CBF and hemoglobin concentration, cerebral oxygen delivery and utilization seem to be maintained in resting subjects with acute hypoxia (72). However, evidence indicates that when hypoxic subjects exercise, brain oxygen saturation falls precipitously. In 1983, using hypoxic gas mixtures to generate a normobaric hypoxia equivalent to 8,000 ft, Paul (65) found that in response to very mild exercise (600 ml O2/min) designed to simulate the workload in an normal cockpit environment during a busy phase of flight, arterial blood oxygen saturation dropped from 89% to 80%. These results were reported by Fowler et al (24) in 1985. Two more recent studies reported exercise-induced decreases in blood oxygen saturation at the higher altitudes of 3,450 m (11,300 ft) (14) and 3,700 m (12,100 ft) (78) respectively. Saito et al (78) reported an exercise-induced drop in blood oxygen saturation of 48% relative to resting values, prompting Roach and Hackett (72) to predict that humans who exercise during acute hypoxia will experience substantial systemic and cerebral oxygen desaturation, and that those with the most severe cerebral desaturation will develop the largest brain swelling and the most severe HAH (high altitude headache) and AMS.

Increased intracranial pressure, as well as edema on autopsy and responsiveness of AMS to steroids has led researchers to speculate that cerebral edema may have a role in the symptomology of AMS (32, 35, 83, 86). The recent emergence of magnetic imaging resonance imaging (MRI) technology is allowing the assessment of whether or not cerebral edema is causal for AMS. Using MRI scans, Hackett et al (36) demonstrated a pattern of reversible white matter edema, especially in the corpus callosum, without any gray matter involvement suggesting a vasogenic rather than a cytotoxic mechanism. While brain edema is an abnormal accumulation of water within the brain parenchyma producing a volumetric enlargement of tissue, brain swelling refers to enlargement of the brain from any cause including elevated cerebral blood volume (CBV), elevated intracranial cerebro-spinal fluid (cCSF) and brain water levels (32, 35, 48). Roach and Hackett (72) hypothesized that as AMS develops, a swollen brain would shunt cCSF out of the cranial space via the fourth ventricle and the aqueduct of Sylvius. They completed some preliminary studies using MRI to assess the role of brain swelling and cerebral edema in early AMS. Their results showed that cCSF decreased in severe and in moderate AMS with a slightly greater drop in cCSF in moderate than in severe AMS. This led them to postulate that craniospinal capacitance plays an important role in determining AMS where the inability to limit brain swelling by moving cCSF to extracranial compartments will lead to AMS (72).

While there are many measurements of CBF in humans during acute hypoxia, measurements of CBV have not yet been carried out. However, in non-human primates a 50% increase in CBF caused a 15% increase in CBV (30). An equivalent volume increase (15%) in a 1500 g human brain would be 6-8 mL. A 6-8 mL in crease in CBV would be sufficient to displace some CSF and would be detectable by neuroimaging (MRI or Computer-aided Tomography (CAT-Scan)) as smaller ventricles and more extracerebral CSF (72). One of the earliest attempts to measure CSF pressure was done in 1933 by Shaltenbrand (80) who found that

CSF pressure began to increase at 3,000 m (9,600 ft) and reached 12 mmHg at 5,200 m (17,100 ft). More recently, Hartig and Hackett (39) exposed 3 subjects to 5,000 m (19,000 ft) measuring their CSF pressure via lumbar catheter which showed only a slight increase in pressure at rest, but markedly elevated pressure during exertion and during periodic breathing with one subject showing a 3-fold increase in CSF pressure (10 mm Hg to 30 mm Hg) with the nadir of the oscillating arterial blood oxygen saturation. This suggested altered brain compliance, such that small increases in CBV caused disproportionate increases in CSF pressure. This was confirmed by measurement in that the increase in CSF pressure for a given increase in CBF was 43% higher at altitude than at sea level. Further, measures that reduced CSF pressure (breathing oxygen and hyperventilation) improved symptoms but increasing CSF pressure by breathing hypoxic gas mixtures made subjects worse (39). These data suggest altered brain compliance could be due either to increased brain water content or to a large increase in CBV linked with a small cerebrospinal capacitance (72).

In summary, intracranial pressure may be elevated by hypoxia alone, but to date the limited data have not confirmed the presence of consistently elevated intracranial pressure in AMS. Current data support the notion that transient increases in intracranial pressure occur upon slight physical exertions that change intracranial pressure. Further, these changes in intracranial pressure and/or CBV seem to be reproducibly related to symptoms of AMS (72).

With respect to understanding individual differences in susceptibility to AMS, the correlation of AMS with hypoxic ventilatory response (HVR), ventilation, fluid status, lung function and physical fitness has been weak at best (72). In 1985, Ross hypothesized that individual differences in susceptibility to AMS might be based on random anatomical differences (76) such that people with a smaller intracranial and intraspinal CSF capacity would be at higher risk to develop AMS given that they would not be able to tolerate brain swelling as well as people with more 'room' in the craniospinal axis. The displacement of CSF via the aqueduct of sylvius into the spinal canal is the first compensatory response to increased brain volume, followed in turn by an increase in CSF absorption and decreased CSF production by the choroid plexus in the cerebral ventricles (72). Shapiro et al. have shown that the increase in intracranial pressure for a given increase in brain volume is directly related to the ratio of the intracranial volume and to the volume of the spinal canal (82). Essentially, the greater the CSF volume, the greater the capacity to attenuate increases in brain volume. Ross points out that if this hypothesis is true, elderly persons should have a reduced incidence of AMS given their enlarged ratio of brain to cranial vault volume because brain size decreases with increasing age (76). In fact, elderly persons have been shown to have a lower incidence of AMS (73) thus lending credence to this hypothesis.

5. Interventions to prevent AMS

By the late 1960s, two lines of pharmacotherapy for combating AMS had emerged; the manipulation on blood pH by treatment with the carbonic anhydrase inhibitor Acetazolamide (15), and diuresis, with powerful diuretics such as furosemide (83). However, in 1971, Gray et al (29) demonstrated the efficacy of acetazolamide and the lack of efficacy of furosemide. Acetozolamide remains a main stream treatment for AMS to this day (9, 62).

Cerebral edema occurs in fatal cases of AMS and Dexamethasone (a corticosteroid) is used to treat cerebral edema from other causes, and also reduces the symptoms of AMS when given prophyactically (54). It can also be given as an emergency treatment when descent to lower altitude is delayed (22, 54). More recently, Bernhard et al. (9) demonstrated the prophylactic efficacy a daily afternoon dose of 500 mg sustained-release acetazolamide and 4 mg of dexamethasone every 12 hours in preventing AMS during ascent.

Clonidine, an alpha blocker is normally used for treatment of hypertension or menopausal flushing and reduces sympathetic outflow to the heart, kidneys and peripheral vasculature. A recent field study demonstrated the efficacy of a daily dose of 0.2 mg clonidine in the prevention of AMS (92).

More evidence that sympathetic activation may be causal in the development of AMS is provided by (26) who showed that AMS severity was reduced in six subjects on propranolol at 4,300 m (14,100 ft).

A recent study has demonstrated that a twice-daily dose of 160 mg EGb 761 (Gingko biloba) is very effective in the prevention of AMS (75). If Gingko biloba is confirmed as a potent prophylaxis for AMS, future studies will need to assess the role of Gingko biloba-induced changes in BBB permeability, changes in CBV and cerebral edema in the onset of the symptoms of AMS (72).

Oxygen, in even in low concentrations has also been shown to be very effective in the prevention of AMS. Recently, in support of mining and scientific operations at high altitude, West (93) has described portable modules with oxygen concentrators which are used for sleeping, living, and laboratory quarters. In these quarters, personnel breathe ambient air and 27% oxygen in order to preclude contracting AMS. An analogous approach to protecting aircrew flying at high cabin altitudes would be the use of low-flow pulse-dose oxygen regulators deliverying oxygen via an oro-nasal cannula.

6. A review of the impact of hypoxia on performance

The minimum altitude at which hypoxia-induced performance decrements are evident has been a controversial issue. However, the most recent evidence suggests that between 8,000 and 10,000 ft. the risk while real, is relatively low.

One of the most studied areas of the behavioural effects of hypoxia has been vision. MacFarland et al. (59) pointed out that the retina is closely related to the brain embryologically, morphologically, physiologically and anatomically, and therefore, has a similar metabolism. It has also been demonstrated that hypoxia profoundly affects vision in a number of ways. A subject exposed to hypoxia experiences a diminution of apparent light intensity in the visual field, followed by a return to normal visions when normal oxygen is restored (59). Brightness sensitivity can be used to discriminate the effects of unprotected exposure to high altitude (58). As far back as the 1930s, McFarland's work demonstrated that vision is very sensitive to the effects of hypoxia, especially at low levels of background illumination (56, 57, 59, 60). In fact, night vision has shown to be impacted at altitudes as low as 4,000 ft (60). This is why WWII bomber crews conducting night operations were encouraged to be on oxygen throughout each mission. A marked decrease in visual acuity has also been found at low levels of background illumination during hypoxia. This effect was much less pronounced with bright backgrounds such as sunlight. The increase in light threshold at 4,752 m (15,000 ft) is approximately 100 percent: twice as much light being required to see a given target under this condition as compare to sea level (58). AT 6,096 m (20,000 ft) the increase in threshold is approximately threefold (60).

Another behavioural aspect of hypoxia concerns its effects on reaction time and movement time. As pointed out by Tune (88), the earlier studies of the effects of hypoxia on 'reaction time' did not discriminate between reaction time (RT) and movement time (MT). It is not clear in one of the earliest studies of hypoxia on 'response time' (56) whether or not the dependent measure was response time (RT + MT) or RT. In any case, McFarland found no significant decrease in simple response time performance below an altitude of 7,163 m (23,500 ft) in this study. No performance decrement was found in a four-choice response time task until reaching an altitude of 5,791 m (19,000 ft). This happened to be to be 1,372 m (4,500 ft) below the altitude at which simple response time was affected in the same subjects (56). Bills (12) used well practised subjects and found an increase in serial choice reaction time at an altitude of 4,572 m (15,000 ft). Ledwith (52) employed a more sensitive design in an effort to separate out the effects of mild to moderate hypoxia on the two components of response time: RT and MT. He found that RT decreased from sea level to 2,134 m (7,000 ft) and returned to the values found at sea level by 4,267 m (14,000 ft), thus yielding a significant quadratic function. MT was found to vary inversely with RT, also in a quadratic function, resulting in only minimal overall change in response time. In this study, Ledwith used a separate groups design, naïve subjects, and the age distribution of the subjects was bimodal. It was concluded that the effects of hypoxia on RT and MT were not clearly interpretable because of the extent of the modification of experimental results by task novelty, anxiety, and subject age. In an attempt to overcome the difficulties encountered by Ledwith, Fowler et al. (25) used a more severe level of hypoxia, 6,700 m (19,000 ft) and well trained subjects with a serial choice response time task, in a design which allowed CRT (choice reaction time) and MT to be assessed separately. The results of this study indicated that CRT was lengthened by a simple increase in reaction time. Fowler et al. proposed that the reason for the change in simple reaction time is that hypoxia may reduce the effective luminant intensity of the

stimulus (red light-emitting diodes (LED), with one LED adjacent each of the 5 reaction time response buttons). Fowler's argument that vision is a likely candidate to explain the impairment in certain other complex tasks (19, 46).

Another area of impact due to hypoxia concerns learning and memory. McFarland (57) tested learning and memory at sea level and at 4,572 m (15,000 ft) and observed significantly poorer learning performance at altitude. Using the same paradigm, Malmo and Finan (55) found progressive memory impairment with increasing altitude starting at 3,810 m (12,500 ft). Russell (77) assessed learning performance using finger dexterity, arm-hand coordination, and an addition task at sea level and 5,486 m (18,000 ft). He found that a decrease in performance within 5 minutes of exposure to altitude for all three tasks, followed by a slight improvement after approximately 15 minutes at this altitude. The difference between immediate and delayed recall of word lists at 3,810 m (12,500 ft) was assessed by Phillips and Pace (68), where the difference in performance between immediate and delayed work recall was taken to represent a measure of long-term memory loss, which was greater for the last 5 serial positions (recency) than for the first five positions for both sea level and altitude. At altitude, it was observed that words presented in the last half of the lists were recalled more poorly, while word in the first half of the lists (primacy) were recalled better than at sea level. This effect was transitory, disappearing in the later stages of practice. These results suggest that short-term memory (STM) is affected by hypoxia but long-term memory (LTM) is not. This is not in agreement with the experiments mentioned earlier. These earlier mentioned studies seem to show that learning (and, by inference, LTM) is affect by hypoxia although the former studies used a more sever hypoxia. Moreover, Ledwith (53) used a dichotic listening task to show that STM was not affected by hypoxia. Further more, Crow and Kelman (18) used a similar procedure as Phillips and Pace, and were unable to demonstrate any differences in recall ability due to hypoxia at the same altitude. Overall, these results can be interpreted as evidence suggesting that hypoxia may affect learning and memory but the specific details remain to be clarified due to the conflicting results discussed above.

During the 1960s and 1970s a debate as to whether or not performance is compromised at 8,000 ft. appeared in the literature. Most of the research that was the subject of this debate originated in England at the R.A.F. Institute of Aviation Medicine in Farnborough which indicated that performance of complex unlearned tasks may be impaired at altitudes as low as 1,524 m (5,000 ft) (11, 19, 28). A similar finding has been reported by Kelman and Crow (46) but has not been confirmed in other studies (18, 47). Ernsting (21) reviewed some of the human performance literature on mild acute hypoxia and concluded that a cabin altitude of 1,829 m (6,000 ft) should be the maximum for both military and civil aircraft operations rather than the previously accepted 2,438 m (8,000 ft). One paper by Dennison, Ledwith and Poulton, (19) using a spatial orientation task (the manikin task) claimed that the ability to learn a novel task was compromised at 5,000 ft, the implication being that well-learned tasks are not effected at 5,000 ft. but responding to a novel situation (such as an emergency) might well be compromised at this altitude. Given the limitations of this paper (only 2 groups of 4 subjects each, and with large inter-subject variability), this work had far too much influence. Our own work at DCIEM, replicated this work using 144 subjects over 4 altitudes (5,000 ft, 8,000 ft, 10,000 ft, and 12,000 ft) and using the same psychomotor test, we found no such effect at any of our test altitudes (67). We concluded that there is no measurable decrement in the ability of naïve subjects to learn either the manikin task or the other two tasks (serial reaction time, and logical reasoning) used in our study at altitudes up to and including 3,660 m (12,000 ft).

7. Conclusions

1. The minimum altitude at which hypoxia-induced performance decrements are evident has been a controversial issue. However, the most recent evidence suggests that between 8,000 and 10,000 ft. the risk while real, is relatively low

2. The risk of developing symptomatic acute mountain sickness (AMS) is very difficult to predict because of large inter-individual differences in susceptibility to AMS and different diagnostic criteria for AMS. However, various studies have demonstrated acute mountain sickness in a significant proportion of individuals in the 8,000-10,000 foot range.

8. Recommendations

1. Given that the literature indicates that Acute Mountain Sickness symptoms can develop within 6 hours of exposure to hypoxia and can develop in some people at altitudes even somewhat lower than 8,000 ft, we recommend that when aircrew are exposed to cabin altitudes between 8,000 ft and 10,000 ft, their time at those altitudes should be limited to 4 hours.

2. Should aircrew be called upon to fly at cabin altitudes greater than 8,000 ft for longer than 4 hours we recommend that supplementary oxygen be provided to them. In order to facilitate aircrew compliance with respect to breathing oxygen they should each be provided a low-flow pulse-dose oxygen system. While there are several different manufacturers of low flow oxygen equipment, in our opinion, the most evolved/effective systems are provided by "Aeromedic Innovations" in the U.K. This is a demand oxygen system delivered through unobtrusive nasal cannulae. Using this system with a portable light-weight carbon storage cylinder, oxygen can be delivered for up to 43 hrs. Given the average return air-time for an Air Transport mission to Bosnia from Trenton (ranges from 29 to 33 hours) such a low flow pulse-dose oxygen system would be more than adequate for these and similar missions.

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